Direct Oral Anticoagulants (DOACs) (formerly called TSOACs)
Dabigatran (Pradaxa), Rivaroxaban (Xarelto), and Apixaban (Eliquis)
Criteria for Use for Stroke Prevention in Nonvalvular Atrial Fibrillation (AF)
January 2014
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. ***THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE OUTSIDE THE RECOMMENDATIONS SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.***

The Product Information should be consulted for detailed prescribing information. The VA National PBM-MAP-VPE DOAC Drug Class Review, individual Drug Monographs, and CFU for Venous Thromboembolism (VTE) Treatment and VTE prophylaxis are available at www.pbm.va.gov or https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx/

Note: Stable patients on warfarin may be effectively maintained on warfarin rather than switching to a DOAC in the setting of good INR control and acceptability to the patient and provider. Internal national VA metrics for August 2014 show 71% of patients receiving warfarin through the VA have an INR between 1.8 and 3.3.

Pivotal Studies Summary:

	DABIGATRAN	RIVAROXABAN	APIXABAN
Pivotal study **DOAC vs. warfarin (INR 2-3)**	RE-LY Open-label	ROCKET-AF Double-blind	ARISTOTLE Double-blind
Mean $CHADS_2$ score	2.1	3.5	2.1
Mean Time in Therapeutic Range (TTR)	64%	55%	62%
Efficacy: Reduction in all stroke, systemic embolism	Superior	Non-inferior	Superior
Safety: Major bleeding	Similar	Similar	Superior
Mortality	Favorable trend	Favorable trend	Superior

No head to head studies of DOACs are available; differences in trial design and patient populations limit the ability to make indirect comparisons between DOACs.

EXCLUSION CRITERIA (if ONE is checked, patient is not eligible)

- ❑ Indication for anticoagulant treatment is other than nonvalvular AF or VTE treatment (see DOAC VTE Treatment Criteria for Use)
- ❑ Prosthetic heart valve (See Issues for Consideration)
- ❑ Clinically significant valvular disease (e.g., moderate to severe mitral valve stenosis)
- ❑ Following acute stroke or TIA[a]
- ❑ Active endocarditis
- ❑ Active pathological bleeding
- ❑ Known significant liver disease (See Issues for Consideration)
- ❑ For dabigatran, concurrent use of a significant P-glycoprotein (P-gp) interacting drug (See Comparative Table for further discussion)
- ❑ For rivaroxaban and apixaban, concurrent use of a significant dual P-gp and CYP3A4 interacting drug (See Comparative Table for further discussion)
- ❑ Previous hypersensitivity reaction to DOAC
- ❑ Pregnancy (i.e., known pregnancy or positive pregnancy test)
- ❑ Breastfeeding
- ❑ Increased bleeding risk: medical condition or history of major bleed that would be considered a contraindication to anticoagulation (See Issues for Consideration).
- ❑ Severe renal impairment[c] (See Comparative Table):
  - Dabigatran: creatinine clearance (CrCl) <30 ml/min
  - Rivaroxaban: CrCl <30 ml/min
  - Apixaban: CrCl <25 ml/min or serum creatinine (SCr) >2.5 mg/dL

INCLUSION CRITERIA

ALL must be selected for patient to be eligible for DOAC:

- ❑ Diagnosis of non-valvular AF or flutter (with AF or flutter documented by electrocardiogram)
- ❑ The decision has been made to use an oral anticoagulant (vs. aspirin or no treatment) in the presence of at least one additional risk factor for stroke (e.g., $CHADS_2$ or CHA_2DS_2-VASc score ≥1[b]) or prior TIA, stroke or systemic embolism.
- ❑ Renal function assessment (CrCl) (see Monitoring for additional information)

Dabigatran is the preferred DOAC in the absence of a compelling rationale for an alternative agent (see algorithm for DOACs and Consideration for Using a DOAC below)

For rivaroxaban (ONE or more of the following additional criteria must be selected for patient to be eligible):

- ❑ Renal impairment (CrCl 30-50 ml/min)
- ❑ Medical or other compelling reason to avoid twice daily medication
- ❑ Unable to swallow whole pills
- ❑ Need for use of a pill reminder box
- ❑ Patient is intolerant to or is not a candidate for dabigatran

For apixaban (ONE or more of the following must be selected for patient to be eligible):

- ❑ Age of 75 years or older
- ❑ Renal impairment (SCr 1.5-2.5 mg/dL or CrCl 25-50 ml/min)
- ❑ Considered at increased risk of bleeding, including GI bleeding[d]
- ❑ Patient is intolerant to or is not a candidate for dabigatran or rivaroxaban

For women of childbearing potential:

- ❑ Determine pregnancy status prior to starting DOAC and provide contraceptive counseling. Discuss potential risk vs. benefit of DOAC treatment during pregnancy. Women taking a DOAC should notify their provider if they become pregnant.

DOSAGE AND ADMINISTRATION

- Usual doses for nonvalvular AF:
  - Apixaban: 5 mg twice daily
  - Dabigatran: 150 mg twice daily
  - Rivaroxaban: 20 mg once daily
- See prescribing information for reduced dosing in special populations
- Due to lack of clinical data, PBM recommends avoiding the use of each DOAC in the following degrees of renal impairment:
  - Apixaban: CrCl <25 ml/min or SCr >2.5 mg/dL
  - Dabigatran: CrCl <30 ml/min or 30-50 ml/min and on interacting drug (dronedarone or ketoconazole)
  - Rivaroxaban: CrCl <30 ml/min

MONITORING

- **Patients should be monitored for adherence, signs and symptoms of bleeding, stroke, and other adverse effects.**
- Prior to starting therapy, it should be assured that the patient does not have anemia or thrombocytopenia and has adequate renal function. In patients with chronic kidney disease or other conditions where CrCl may fluctuate or in patients >75 yrs of age, monitoring of serum creatinine and estimating CrCl should be performed more frequently at the discretion of the provider; therapy should be adjusted as needed.
- No routine laboratory monitoring of anticoagulant activity is recommended.

ISSUES FOR CONSIDERATION

- **Discontinuation of therapy:** Patients are at increased risk of thrombotic events (e.g., stroke) when the DOAC is discontinued in the absence of alternative anticoagulation based on data from ARISTOTLE (apixaban) and ROCKET AF (rivaroxaban). If the DOAC must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant.
- **Prosthetic heart valves:** Dabigatran, an oral direct thrombin inhibitor, is associated with an increased risk of adverse outcomes (e.g., valve thrombosis, stroke, myocardial infarction [MI], bleeding) in patients with mechanical prosthetic heart valves. Patients with mechanical prosthetic heart valves were excluded from the pivotal clinical trials with apixaban and rivaroxaban. Because of the known adverse outcomes with a related agent (dabigatran) and the lack of data available with apixaban and rivaroxaban, DOACs should not be used in patients with prosthetic mechanical heart valves. Use of these agents in the setting of other forms of valvular disease, including the presence of a bioprosthetic valve, has not been specifically studied and is not recommended.
- **Contraindications due to increased bleeding risk:** Risk and benefit assessment for individual patients should be conducted. Some of the following examples may be considered relative contraindications depending on the patient scenario: anemia (hemoglobin <10 g/dL) or thrombocytopenia (platelet count <100,000/uL), cancer considered to be at risk for bleeding based on the type of cancer and/or type of cancer treatment being administered, history of intracranial, intraocular, spinal, retroperitoneal, atraumatic intra-articular bleeding, or gastrointestinal bleeding, uncontrolled hypertension (persistently elevated systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg), recent and concomitant treatment with fibrinolytic agent (refer to prescribing information [PI]), or chronic treatment with a nonsteroidal anti-inflammatory drug (NSAID).
- **Use in Significant Liver Disease:** see PI for details. Language in the product label and from the exclusion criteria of the pivotal trials differ between agents. Overall, avoid DOAC use in patients with moderate-to-severe impairment - e.g., acute clinical hepatitis, cirrhosis, liver enzyme elevations (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]) >2-3x upper limit of normal, or hepatic disease associated with coagulopathy.
- **Dabigatran 75 mg twice daily dose:** Dabigatran is eliminated primarily through the kidneys. Based on pharmacokinetic modeling, a reduced dose of dabigatran (75 mg twice daily) was FDA approved for use in patients with CrCl 15-30 ml/min; however, there are no clinical data evaluating the use of the reduced dose, as patients with CrCl <30 ml/min were excluded from the pivotal RE-LY study. PBM recommends avoiding the use of dabigatran 75 mg twice daily in the absence of safety and efficacy data and the availability of alternatives (i.e., warfarin).
- **Pharmacodynamic Interactions:** Concomitant use of DOACs and medications that affect hemostasis are expected to increase the risk of bleeding (aspirin, anti-platelet agents, other anticoagulants, fibrinolytics, nonsteroidal anti-inflammatory drugs (NSAIDs). Low dose aspirin (≤165 mg/day) combined with DOACs (or warfarin) increases the risk of bleeding. In acute coronary syndrome (ACS) populations, the addition of apixaban (full dose), rivaroxaban (low dose), or dabigatran (varying dose) to aspirin plus a $P2Y_{12}$-receptor antagonist (e.g., clopidogrel) was found to significantly increase bleeding risk. The need for concurrent use of anti-platelet medications or other medications that may increase the risk of bleeding should be re-evaluated when a DOAC is prescribed.
- **Reversal of anticoagulant effects:** Idarucizumab is a reversal agent specific for dabigatran only. There is no reversal agent for rivaroxaban or apixaban, although the DOACS have a relatively short duration of action compared to warfarin. Information on the optimal management of bleeding with DOACs is lacking. Management should be individualized according to the specific situation but may reasonably include discontinuation of treatment and implementation of supportive measures (compression, surgical hemostasis, transfusion). Dialysis may be effective for dabigatran but is not expected to be effective for removal of apixaban or rivaroxaban (given the high protein binding of the drugs). Activated charcoal may reduce absorption of the DOACs and may be considered in cases of suspected overdose or bleeding if administered within 2 hours of the last DOAC dose.
- **Switching from or to warfarin:** When switching from warfarin to a DOAC, prescribing information recommends starting DOAC when INR is < 3 (for rivaroxaban) and < 2 (for dabigatran and apixaban). DOACs reach therapeutic effects within a few hours. When converting from DOAC to warfarin, consider that DOACs affect INR. If continuous anticoagulation is needed, discontinue DOAC and start a parenteral anticoagulant with warfarin at the time the next scheduled DOAC dose would have been due. (See "Discontinuation of therapy" or Boxed Warning in prescribing information on the increased risk of thrombotic events)
- **Switching from or to anticoagulants other than warfarin:** Discontinue the anticoagulant being used and start the other at the next scheduled dose.
- **Interruptions in therapy for surgery and interventions:** If possible, DOACs should be discontinued at least 24 hours prior to surgery or invasive procedures with an increased bleeding risk. Discontinuations of longer durations are recommended for surgery and procedures with a higher bleeding risk where complete hemostasis is required and for patients with renal impairment. Recommendations regarding alterations in anticoagulant therapy for dental procedures can be found at the American Dental Association at: http://www.ada.org/2526.aspx. The risk of thromboembolism off anticoagulation and the risk of peri-procedural bleeding need to be considered (See PIs and Comparative Table for additional, more specific information).
- **Pregnancy:** PBM recommends generally avoiding the DOACs during pregnancy because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible.
- **Coronary Artery Disease:** Dabigatran was associated with a small but consistently elevated risk of myocardial infarction (MI)/acute coronary syndrome (ACS) in clinical trials. Overall, there appears to be about a 30% relative increase in MI/ACS that translates to about a 0.2-0.3% annual absolute increase in events with dabigatran. No excess of MI/ACS with rivaroxaban or apixaban has been observed.
- **Altered gastrointestinal absorption:** There are no clinical data evaluating the DOACs in patients with prior bariatric surgery, gastric bypass, or other procedures or

conditions where gastrointestinal absorption could be significantly altered.

- **Adherence to drug regimen:** Patients should be able to adhere to a twice daily drug regimen with dabigatran and apixaban and to a once daily regimen with rivaroxaban. Adherence rates were very high with the DOACs in the pivotal nonvalvular AF trials, and it is unclear how outcomes may be affected with lower adherence rates, given their relatively short half-lives.
- **Dual care patients:** All patients receiving the drug from VA should be managed according to the same standards (e.g., eligibility, monitoring, follow-up), consistent with the VHA National Dual Care Directive 2009-038.

[a]Adequate data are not available to address the optimal timing of initiation of anticoagulation following a cardioembolic stroke. Available guidance from the American College of Chest Physicians (CHEST 2012) and American Heart Association and American Stroke Association (ASA/AHA 2014) suggest that oral anticoagulation be initiated within 2 wks of acute stroke; however, when there is a high risk of hemorrhagic conversion (i.e., large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhage tendency), additional delays may be appropriate. In contemporary pivotal trials evaluating the new oral anticoagulants, patients were generally excluded from treatment if they had any stroke in the previous 7-14 days, a severe disabling stroke within the previous 3 mos, or a TIA within the past 3 days.

[b]Use of a predictive index for stroke risk assessment is recommended (e.g., $CHADS_2$, CHA_2DS_2-VASc). Sum points for score; risk of stroke increases with higher score. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) AF Guidelines give preference to the CHA_2DS_2-VASc score.

[c]In the pivotal nonvalvular AF clinical trials with the DOACs, CrCl was estimated using the Cockcroft-Gault equation (and using actual body weight in the dabigatran and rivaroxaban trials). Dabigatran is primarily eliminated by the kidneys and has not been studied in a reduced dose for patients with significant renal impairment. Rivaroxaban and apixaban are less dependent on renal elimination than dabigatran and have been studied in reduced doses for patients with significant renal impairment. For patients with a CrCl of 30-50 ml/min, providers may reasonably prefer to use an alternative to dabigatran, particularly if the patient's renal function may fluctuate.

[d]Examples of factors that increase bleeding risk include advanced age, renal impairment, history of bleeding, concomitant use of meds that affect bleeding, hypertension, prior stroke, and anemia. Several bleeding risk score systems that were developed for warfarin (e.g., HAS_BLED, Outpatient Bleeding Risk Index, $HEMORR_2HAGES$) are available, though their predictability has been shown to be limited.

$CHADS_2$ assessment (JAMA. 2001;285(22):2864-70.)

Criterion	Score
Congestive heart failure	1
Hypertension	1
Age ≥75 yrs	1
Diabetes mellitus	1
Stroke or transient ischemic attack	2

CHA_2DS_2VASc assessment (Stroke. 2010;41(12):2731-8.)

Criterion	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75 yrs	2
Diabetes mellitus	1
Stroke or transient ischemic attack	2
Vascular disease (prior MI, peripheral arterial disease, or aortic plaque)	1
Age 65-74 yrs	1
Sc (Sex category) female gender	1

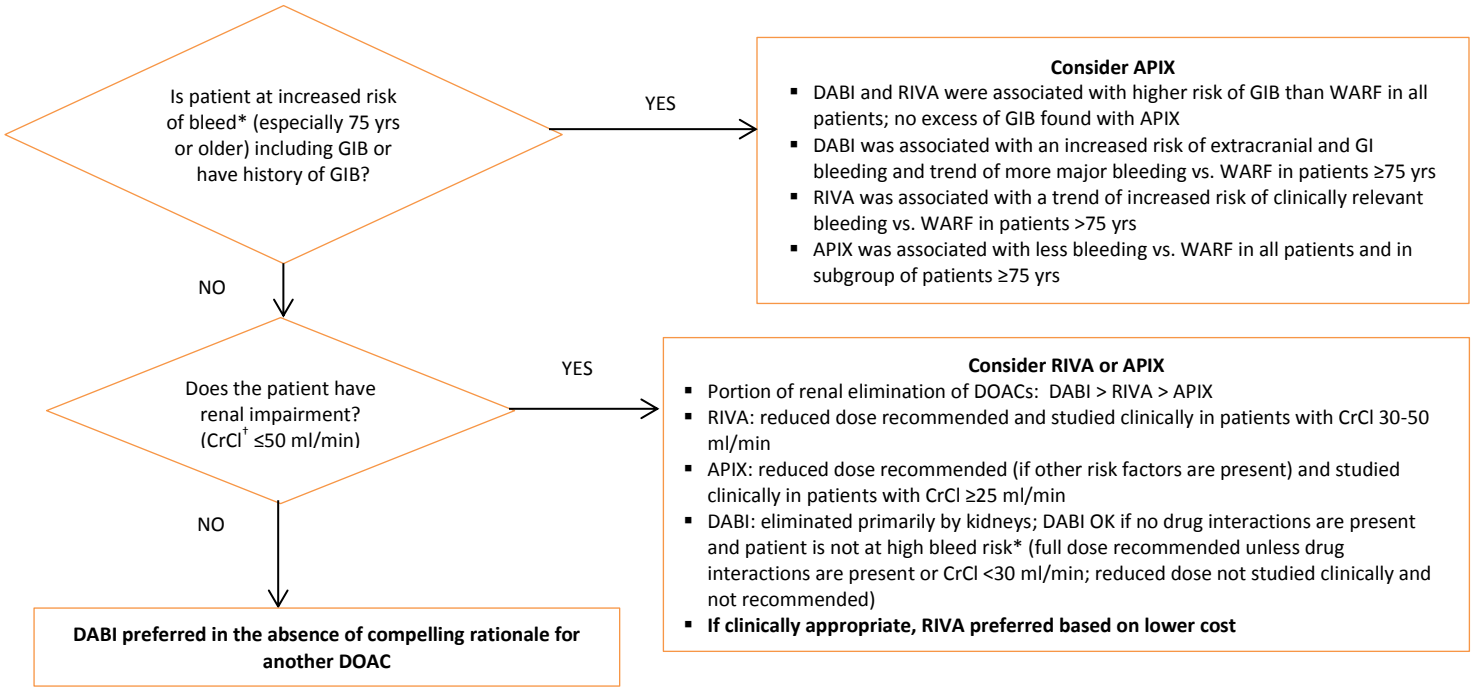
Anticoagulation Algorithm – Considerations for Selection of Target-Specific Oral Anticoagulants (DOACs) for Nonvalvular Atrial Fibrillation (NVAF) in VA Patients

Patient with NVAF and decision to use anticoagulant has been made

Target Specific Oral Anticoagulant (DOAC) or warfarin (WARF)?

- WARF and DOACs are acceptable 1st line agents
- DOACs not recommended and WARF should be used in patients with the following:
  - CrCl <30 ml/min or end stage renal disease (ESRD) on dialysis
  - Prosthetic heart valve
  - Additional indication for anticoagulation other than venous thromboembolism (VTE) history
  - On concomitant therapy with interacting drugs
- WARF may be effectively initiated or continued in the setting of good INR control and acceptability to patient and provider
- DOACs may be useful in the setting of poor INR control on WARF despite adherence, difficulty obtaining regular INR checks, and drug interactions that can't be managed by adjusting WARF dose

Decision to use DOAC has been made
(Consider all clinical factors prior to final drug selection)



Consider APIX

- DABI and RIVA were associated with higher risk of GIB than WARF in all patients; no excess of GIB found with APIX
- DABI was associated with an increased risk of extracranial and GI bleeding and trend of more major bleeding vs. WARF in patients ≥75 yrs
- RIVA was associated with a trend of increased risk of clinically relevant bleeding vs. WARF in patients >75 yrs
- APIX was associated with less bleeding vs. WARF in all patients and in subgroup of patients ≥75 yrs

Consider RIVA or APIX

- Portion of renal elimination of DOACs: DABI > RIVA > APIX
- RIVA: reduced dose recommended and studied clinically in patients with CrCl 30-50 ml/min
- APIX: reduced dose recommended (if other risk factors are present) and studied clinically in patients with CrCl ≥25 ml/min
- DABI: eliminated primarily by kidneys; DABI OK if no drug interactions are present and patient is not at high bleed risk* (full dose recommended unless drug interactions are present or CrCl <30 ml/min; reduced dose not studied clinically and not recommended)
- **If clinically appropriate, RIVA preferred based on lower cost**

DABI preferred in the absence of compelling rationale for another DOAC

Notes:

- **The algorithm is not all inclusive, and complex patients may not fit the algorithm. Clinical judgment should be used.**
- No head to head studies between DOACs have been conducted; considerations for one agent over another are based on data from pivotal trials with a DOAC vs. warfarin or on indirect comparisons of DOACs.
- See comparative table for more information
- Patients with CAD: DABI is associated with a small but significant increased risk of MI when data are considered in total. It is not known whether patients with CAD are at higher risk of events with DABI. Triple therapy (ASA, $P2Y_{12}$ antagonist and anticoagulant) is associated with increased bleeding vs. dual antiplatelet therapy
- RIVA is the only once daily DOAC and may be considered in patients with medical or other reason to avoid twice daily dosing

APIX=apixaban; CAD=coronary artery disease; CrCl=creatinine clearance; DABI= dabigatran; DVT=deep vein thrombosis; GIB= gastrointestinal bleed; INR=international normalized ratio; PE=pulmonary embolism; RIVA= rivaroxaban; WARF=warfarin; VTE=venous thromboembolism

* Examples of factors that increase bleeding risk include advanced age, renal impairment, history of bleeding, concomitant use of meds that affect bleeding, hypertension, prior stroke, and anemia. Several bleeding risk score systems that were developed for warfarin (e.g., HAS_BLED, Outpatient Bleeding Risk Index, $HEMORR_2HAGES$) are available, though their predictability has been shown to be limited.

† CrCl was estimated using the Cockcroft-Gault equation in the pivotal clinical trials of DOACs (and using actual body weight in the dabigatran and rivaroxaban trials).

COMPARATIVE TABLE: CONSIDERATIONS IN CHOICE OF ORAL ANTICOAGULANT FOR NVAF

	DABIGATRAN	RIVAROXABAN	APIXABAN	WARFARIN
Dosing	150 mg BID	20 mg once daily	5 mg BID	Variable dose; once daily
Special considerations	Caps cannot be crushed or opened	Cannot be administered via feeding tube placed distal to stomach	None	None
Dietary considerations	Take with full glass of water	Must take with meal for adequate absorption	None	Steady intake of Vitamin K containing foods
Renal impairment *Note: The VA PBM recommendations for renal dosing are based on evidence from the pivotal clinical trials and may differ from information provided in the package label.*	Primarily renal elimination	~1/3 renal elimination	~1/4 renal elimination	Minimal renal elimination
	PBM recommendations: ***Note: 75 mg BID dose not recommended*** **Avoid if CrCl <30 ml/min (not studied)** **Avoid if CrCl ≤50 ml/min and if on concomitant dronedarone or systemic ketoconazole**	**PBM recommendations:** **Avoid if CrCl <30 ml/min (not studied)** **Reduced dose of 15 mg once daily for patients with CrCl 30-50 ml/min (studied and FDA approved)**	**PBM recommendations:** **Avoid if SCr >2.5 mg/dL or CrCl <25 ml/min (not studied)** **Reduced dose of 2.5 mg BID if patients have 2 or more:** ▪ **SCr ≥1.5 mg/dL** ▪ **≥80 yrs** ▪ **wt ≤60 kg** **(studied and FDA approved)**	n/a
	Package Labeling: Reduced dose of 75 mg BID if CrCl 15-30 ml/min Reduced dose of 75 mg BID if CrCl 30-50 ml/min AND on concomitant dronedarone or systemic ketoconazole. No recommendations for CrCl <15 ml/min or dialysis	Package Labeling: Reduced dose of 15 mg once daily if CrCl 15-50 ml/min Avoid if CrCl <15 ml/min	Package Labeling: Reduced dose of 2.5 mg BID if patients have 2 or more: ▪ Age ≥80 yrs ▪ Wt ≤60 kg ▪ Serum creatinine ≥1.5 mg/dL End stage renal disease and on stable hemodialysis: ▪ 5 mg BID if age <80 yrs and wt >60 kg ▪ 2.5 mg BID if age ≥80 yrs or wt ≤60 kg	n/a
Prosthetic Heart Valve	Data showing increased adverse outcomes in mechanical prosthetic valves; contraindicated; not recommended for other valvular disease	Not studied and not recommended	Not studied and not recommended	OK
Geriatric Patients	Increased bleeding vs. warfarin in pts ≥75 yrs There are no data on safety and efficacy of using a reduced dose of 75 mg BID empirically in elderly; PBM does not recommend	Trend of increased bleeding in pts >75 yrs	No increase bleeds vs. warfarin Reduce dose of 2.5 mg BID available if ≥2 high risk factors present: age ≥80 yr, wt ≤60 kg, SCr ≥1.5 mg/dL	Less bleeding vs. DABI and RIVA. Consider lower initiation dose and greater sensitivity to dose/INR response in elderly
PUD/GI issues	Increased risk of GIB vs. warfarin Increased GI adverse effects (e.g., dyspepsia, gastritis), more DCs due to adverse effects, esp in beginning of treatment	Increased risk of GIB vs. warfarin	No increased GIB found vs. warfarin	Less GIB vs. DABI and RIVA
Additional indications for anticoagulation	FDA approved for: ▪ VTE treatment ▪ VTE prophylaxis in hip replacement surgery	FDA approved for: ▪ VTE treatment ▪ VTE prophylaxis in orthopedic surgery	FDA approved for: ▪ VTE treatment ▪ VTE prophylaxis in orthopedic surgery	Several indications for use
CAD considerations	Numerical increase in MI vs. warfarin 30% relative increased risk; 0.2-0.3% per yr absolute increase in MI/ACS events	None	None	None

(Cont'd)	DABIGATRAN	RIVAROXABAN	APIXABAN	WARFARIN
ASA/thienopyridine concomitant use	Increased bleeding Little data on ASA+thienopyridine in AF; Increased bleed with unknown benefit in Phase 2 study of ACS pts	Increased bleeding No data on ASA+thienopyridine in AF; Increased bleed with benefit in ACS pts (low dose rivaroxaban)	Increased bleeding No data on ASA+thienopyridine in AF; Increased bleed without benefit in ACS pts	Increased bleeding
Drug interactions	Prodrug is substrate of P-gp AVOID use P-gp inducers (e.g., rifampin, St. John's Wort)- reduced dabigatran effect Caution with P-gp inhibitors (e.g., dronedarone, ketoconazole); AVOID in concurrent renal impairment	CYP3A4, P-gp substrate AVOID use with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort) – reduced rivaroxaban effect AVOID use with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir and ritonavir combinations)- increased rivaroxaban effect	CYP3A4, P-gp substrate AVOID use with strong P-gp and CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort) – reduced apixaban effect Reduced dose of apixaban 2.5 mg BID available for use with strong P-gp and CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, and ritonavir combinations) – increased apixaban effect	Alterations in plasma protein binding; CYP2C9, 1A2, 3A4 induction or inhibition; antibiotics, antifungals, herbals
Cardioversion	Post-hoc, retrospective analysis, small retrospective cohort study: low thromboembolic and bleed event rates in both DABI and WARF groups; case reports of thromboembolic events	Prospective, open-label RCT, small retrospective cohort study; low rates of embolic and bleeding events with RIVA and WARF; post-hoc combo analysis of cardioversion and ablation pts; no difference in outcomes with RIVA vs. WARF in small number of pts	Post-hoc; analysis showed no thromboembolic events and low rates of bleeding outcomes in both APIX and WARF groups	Standard of care
Ablation	Low quality data; most but not all studies suggest similar thromboembolic/ bleeding risk	Very limited data; published combined analysis of cardioversion and ablation pts; no difference in outcomes with RIVA vs. WARF in small no. of pts	No data	Good data; standard of care
Switching from WARF	Start DOAC when INR <2	Start DOAC when INR <3	Start DOAC when INR <2	n/a
Switching to WARF	DABI affects INR	RIVA affects INR	APIX affects INR	n/a
Surgery and Invasive Procedures *The risk of thromboembolic events vs. peri-op bleeding should be considered with use of anticoagulant therapy; expert consultation may be warranted.*	(From PI) Discontinue 1-2 days (if CrCl ≥50 ml/min) or 3-5 days (CrCl <50 ml/min) before invasive procedures or surgery. Consider longer times for higher risk procedures where complete hemostasis is required.	(From PI) Discontinue at least 24 hrs before surgery or procedures with increased bleeding risk.	(From PI) Discontinue at least 24 hrs prior to surgery/procedures where risk of bleeding is low and could be easily managed. Discontinue at least 48 hrs prior to surgery/procedures with moderate to high bleeding risk.	Depending on risks of bleeding with the procedure and thromboembolic events off of anticoagulation, warfarin may be held and bridge therapy with parenteral anticoagulant considered.
Anticoagulant Lab testing	None routinely recommended; if urgently needed, aPTT, TT (qualitative estimate; presence or absence)	None routinely recommended; if urgently needed, PT, anti-Factor Xa (qualitative estimate; presence or absence)	None routinely recommended; if urgently needed, anti-Factor Xa (qualitative estimate; presence or absence)	INR
Anticoagulant Reversal	Idarucizumab *specific* reversal agent for dabigatran only; discontinue drug, provide supportive care. Hemodialysis may be effective.	No reversal agent; discontinue drug, provide supportive care.	No reversal agent; discontinue drug, provide supportive care.	Vitamin K, 4-factor prothrombin complex concentrate (PCC) for life threatening bleeding